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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,438	11/14/2001	David Botstein	10466/201	2374

35489 7590 10/19/2005

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EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 10/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,438	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/3/05, 8/2/05*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124,125 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124,125 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/2/05 has been entered.

Inventorship

In view of the papers filed 2/3/05, the inventorship in this nonprovisional application has been changed by the deletion of A. Ashkenzai, K. P. Baker, L. Desnoyers, D.L. Eaton, N. Ferrara, S. Fong, H. Gerber, J. C. Grimaldi, I. J. Kljazin, M. A. Napier, J. Pan, N. Paoni, D. Tumas, Z. Zhang, M. E. Gerritsen, T.A., Stewart. C. K. Watanabe and P. M .Williams.

Response to Amendment

The Declaration of Goddard et al. under 37 CFR 1.132 filed 02 August 2005, is insufficient to overcome the rejection of claims 124, 125 and 129-131 based upon 35 USC § 101 and 112, first paragraph, as set forth in the last Office action because: it does not establish that the amplification of the encoding nucleic acid in tumors is sufficient to establish utility or enablement for the nucleic acid or encoded protein as discussed below.

Response to Arguments

The rejection of claims under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claims.

Claim Rejections - 35 USC § 101 and 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 124, 125 and 129-131 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons previously set forth and as recast here.

The instant claims are drawn to a polypeptide of SEQ ID NO:33, which is encoded by the nucleic acid of SEQ ID NO:32 or the full-length coding sequence of the cDNA of ATCC 209790. Since the last Office action, the finding of utility has been withdrawn for the encoding nucleic acid in a related case. However, the claimed polypeptide was and remains rejected for a lack of utility and enablement. The reason that the nucleic acid lacks utility is that the significance of the ΔCt was based on the use of normal controls of genomic DNA from human blood (pages 547-548 of the specification) and did not take into account controls for aneuploidy of the tumor tissue used. At page 545, Ct is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification indicates that Ct is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results" It is noted that the ΔCt values at page 550 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.63), and (b) that only one sample, "LT19", gave values that were consistently at least 2. Given the paucity of information, the data do not support the implicit conclusion of the specification that PRO290 polynucleotide shows a positive correlation with lung SqCCa or other cancer. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Thus, the data do not support the implicit assertion that PRO290 polynucleotide or polypeptide can be used as a cancer diagnostic.

While the nucleic acid showed slight amplification in tumor cells, particularly lung squamous cell carcinomas, compared to normal tissue, this does not support a diagnostic use of the nucleic acid for detection of cancerous tissue. Hittelman (Ann. NY Acad. Sci., 952:1, 2001) showed that chromosomal polysomy occurred with a much greater likelihood in cancerous compared to adjacent normal epithelium (p. 6, third paragraph). That means an increased copy number for PRO290 in lung tumors tested was less likely due to an increase unique to PRO290 DNA, but rather due to a more general phenomenon of polysomy of the DNA in epithelial cancers. Additionally, it was also found that, "[T]he presence or absence of squamous metaplasia at biopsy site does not necessarily correlate with the degree of underlying genomic instability," (p. 8, second paragraph). Further, in individuals who had stopped smoking, chromosomal instability was still evident despite the decrease risk of lung cancer, drawing the conclusion that "individuals are differentially sensitive to carcinogenic insult," (p. 8, end of third paragraph). Because of the above considerations, significant further research would have been required of the skilled artisan to determine whether PRO290 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial or specific.

Further, even if the polynucleotide had utility as a tumor marker, the claimed encoded polypeptide has no such utility since there is no reasonable expectation that there is alteration of polypeptide sequence or amount in colon or lung *versus* normal colon or lung tissue. In this instance, the encoded polypeptide cannot bring utility to the encoding polynucleotide or *vice versa*. It is not known what the protein does or if the level of the protein of SEQ ID NO:33 in colon or lung tumors corresponds to mRNA transcript level. There are several valid reasons to support the unpredictability of correspondence between nucleic acid and protein expression, including: differences in mRNA lifetime, protein translation efficiencies, protein stabilities and amount of protein post-translational modification. For example, Haynes et al. (Electrophoresis 19:1862-1 87 1 , 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. l 863, second paragraph, and Figure 1). Haynes et al. used

yeast as an art-accepted model for eukaryotic systems. Lian et al. (Blood 1 :513-524, August 2001) examined mRNA *versus* protein levels in differentiating myeloid cells (MPRO cells), concluding (p. 514, end of 2nd full paragraph) that, "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels...." In the discussion, Lian et al. note (p. 522, first sentence of each of last two paragraphs), "The discrepancies between mRNA and protein levels in MPRO cells appear to be substantially larger than those observed for yeast. Possible causes for the discrepancies include translational regulation, differential expression of certain mRNAs at various stages of cell growth in vitro, post-translational protein modification that varies with the state of maturation of the cells, and selective degradation or excretion of proteins in vivo.... The initial studies of protein expression presented here provide a cautionary note for efforts to interpret cell composition and function in relation to mRNA levels." In a separate comparison by Fessler et al. (J. Biol. Chem. 277(35): 31291-302, Aug. 2002) examining lipopoysaccharide-activated neurophils (col. 2, beginning of last paragraph on p. 31300) they state, "Parallel use of DNA microarrays and proteomics affords a powerful strategy for comparison of corresponding mRNA transcripts and proteins, thereby affording new insights into mechanisms by which the cell regulates its signaling response to the external environment. Of interest, a poor correlation was also found between corresponding transcripts and proteins (Table VIII), as reported in other systems." They warn (first sentence p. 31296), "Nevertheless, the reliance upon DNA microarrays alone affords insight only into the transcriptional response without corroboration at the protein levels."

The claims are drawn to a polypeptide. The specification asserts a number of utilities for both the polypeptide and encoding polynucleotide, however, these utilities are not specific and substantial or well established. For example, in Example 144, it is asserted that the polypeptide may be used as an antigen to make antibodies. Because neither the physiological nor the clinical significance of the polypeptide is disclosed, and because the prior art does not support a very close structural relationship to a disclosed well described family of known proteins disclosed in the specification by both structure and function, the polypeptide and encoding polynucleotide do not have utility as required by 35 USC 101. If the polypeptide antigen does not have utility, then the antibody which binds it (or method of making the antibody) does not have a specific and substantial utility.

Another example of utility is in drug screening and rational drug design (Examples 146 and 147, respectively). The methods involve screening for "agents which can affect a PRO polypeptide-associated disease or disorder" (p. 521, line 32). No disease or disorder is known to be associated with the encoding polynucleotide or encoded polypeptide. In order to discern a utility for the claimed polypeptide through drug screening in the absence of guidance about which type of disease or disorder the encoding polynucleotide or encoded polypeptide causes or how its involvement could lead to treatment, screening for drugs by using the polynucleotide or encoded polypeptide would still require further and undue experimentation to determine the significance of an agent that somehow influenced the polynucleotide's or polypeptide's function.

It is asserted that the encoding PRO polynucleotide can be used in tissue typing or chromosome marking. This asserted utility is not specific or substantial. All genes have a chromosomal location and, with the exception of a few housekeeping genes, have a tissue specific pattern of expression. Thus virtually any polynucleotide can be used in chromosomal marking or tissue typing. Therefore, the asserted utility is not specific to PRO290. The encoded polypeptide likewise cannot have a specific utility based on tissue typing.

Lastly, in Figure 22 of the instant application, it is indicated that the polypeptide has an N-glycosylation site and N-myristoylation sites, cAMP and cGMP-dependent protein kinase phosphorylation sites and tyrosine kinase phosphorylation sites; however, none of these sites alone or in combination provides sufficient information for the skilled artisan to readily identify a specific and substantial use for the polypeptide.

For these reasons, there is no substantial and specific utility for the claimed polypeptide.

Claims 124, 125 and 129-131 remain also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons previously set forth and as recast here, one skilled in the art clearly would not know how to use the claimed invention.

It would require significant further experimentation to be able to use the claimed polypeptide because no particular function or specifically associated disease has been determined for the encoding polynucleotide of SEQ ID NO:32 or encoded polypeptide of SEQ ID NO:33, and there is no disclosed definite function supported by the prior art. No function can be reasonably assigned based on its homology to another polynucleotide(s) or polypeptide(s). Using the claimed polypeptide would require undue experimentation.

Applicants arguments are directed to both the rejection under 35 USC 101 and 112, first paragraph, enablement, and will be addressed here together.

At pages 3-4 of Applicants' response, it is argued that the data in Example 170 (starting at p. 539 of the specification) describes results of a gene amplification assay. Applicants characterize the assay as being capable of quantitatively measuring the level of gene amplification in a sample. Applicants assert that gene amplification is an essential mechanism for oncogene activation. Applicants review how the assay was performed, and reports that the gene encoding PRO290 was significantly amplified (2.297-fold to 4.2-fold) in 5/19 lung tumors. This has been fully considered but is not found to be persuasive. First, it is important to note that

the gene encoding PRO290 was not found to be amplified in 14 out of nineteen lung tumors (6/11 SqCCa-type tumors) and 15/17 colon tumor samples. Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (bottom of p. 547). The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy (see Sen, Hittelman). Given these details, one skilled in the art would not conclude that the gene encoding PRO290 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed polypeptides, since a small amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA and polypeptide levels (see Pennica et al., Konopka et al., Haynes et al, Lian et al., Fessler et al. and Hu et al.).

On p. 4 and p. 6, Applicants refer to the declaration of Dr. Goddard, submitted under 37 C.F.R. § 1.132 on 02 August 2005, as a copy from different case (09/903,925). Applicants quote from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Applicants conclude that one skilled in the art would consider the 2.297-fold to 4.2-fold amplification of the gene encoding PRO290 in 5 lung tumors is significant and credible based upon the facts in the Goddard declaration. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.297- to 4.2-fold amplification of the gene encoding PRO290 in five lung tumors is significant and credible. Credibility has never been questioned. However, the significance can be questioned since 14 out of nineteen lung tumor (6/11 SqCCa-type tumors) and 15/17 colon tumor samples did not show an amplification of the gene encoding PRO290, and the control used

was not a matched non-tumor lung or colon sample, respectively, but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). Hu et al., Pennica et al., Konopka et al., Haynes et al., Lian et al., and Fessler et al. speak to the strength of the opposing evidence as discussed in the previous Office and in the rejection above. The expert has interest in the outcome of the case since Dr. Goddard is listed as an inventor and is employed by the assignee. Finally, the expert refers to three publications as factual support for the conclusions in the declaration. However, neither Livak et al. nor Heid et al. appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors. Pennica et al. was found to support the rejection, as discussed above. The Goddard declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO290 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, the PRO290 gene has *not* been shown to be useful to track the efficacy of cancer therapy. The specification merely demonstrates that the PRO290 genomic DNA may be amplified in some cancers, to a minor degree (about 2.5 fold) compared to normal DNA from blood. No mutation or translocation of PRO290 has been associated with any type of cancer versus normal tissue. It is not known whether PRO290 is amplified in corresponding normal tissues, and what the relative levels of amplification are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO290 may be amplified in a variety of samples and invites the artisan to determine the significance of this increase. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment. Based on consideration of the evidence as a whole, the rejection is proper.

In the middle of p. 4, Applicants argue that it is well known that gene amplification occurs in most solid tumors, including lung carcinomas, and is generally associated with poor prognosis. Applicants conclude that the PRO290 gene becomes an important diagnostic marker to identify malignant lung carcinomas, even when the lung malignancy associated with PRO290 molecule is a rare occurrence. This has been fully considered but is not found to be persuasive. As discussed in the rejection above, gene amplification is common in non-cancerous colon and lung epithelium based on the damage the epithelium suffers from exposure to the environment.

See Sen and Hittelman et al. There is no control for non-cancerous lung tissue, and thus the relevance of the data in the specification is not clear. Furthermore, there is no disclosure of a correlation of amplification with tumor formation, progression, severity, etc., all of which would speak to prognosis.

Applicants argue (pages 4-5) that the standard for utility is that it is "more likely than not" that the asserted utility is specific and substantial and that the Office did not present evidence to establish that there is not a reasonably expectation that the encoded polypeptide has utility (*i.e.*, is useful as a diagnostic tool in certain cancers). It is also argued that the Examiner has not presented a *prima facie* case for lack of utility. The argument has been fully considered, but is not persuasive. While one can find prior art that supports a "significant probability" that mRNA and protein levels will correlate, there is influential art of record that requires the Examiner maintain that as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:32 positively correlates with the expression of the protein of SEQ ID NO:83. This is particularly true of genomic DNA. The advent of proteome analysis has begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma. As stated in the Office action mailed 11/9/04, "For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a micoarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease." Indeed, there is evidence in the art to refute generalizations about gene/protein correlations. For example, Haynes et al. (Electrophoresis 19 : 1862-1 87 1 , 1998, previous cited) as discussed above showed from studies with yeast that among 80 proteins studied which were relatively homogenous in half-life and expression level, no strong correlation existed between protein and transcript levels. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1 863, second paragraph, and Figure 1). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating

that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). Pennica et al. (1998, PNAS USA 95:14717-14722), show a lack of correlation between gene amplification and overexpression in two out of three WISP genes. Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) state that polypeptide expression correlated with mRNA levels, but not gene amplification for the abl gene. Even if increased mRNA levels could be established for PRO290, it does not follow that polypeptide levels would also be amplified. Given how small the amount that DNA copy number of PRO290 increased in tumors and that it increased in only a minority of lung and colon tumors, and the evidence provided by Haynes et al., Hu et al., Fessler et al., Lian et al., Pennica et al. and Konopka et al., one skilled in the art would not have assumed that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. The level of increase of the encoding nucleic acid is not disclosed. One skilled in the art would have to do further research to determine whether or not the PRO290 polypeptide levels increased significantly in the tumor samples. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

As was stated above, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the

specification has not provided the invention in a form the skilled artisan could use without significant further research.

Applicants argue (pages 6-7) that the fact that 5 out of 19 lung tumor samples and 2 out of 17 colon tumor samples tested positive in the gene amplification assay does not make the gene amplification data less significant or spurious. Applicants reasons that some tumor markers are useful for identifying rare malignancies. Applicants argue that such rare tumor markers have great value in tumor diagnosis, prognosis, and classification of tumors. Applicants conclude that it is not relevant to utility whether the PRO290 gene was amplified in five lung tumors or most lung tumors sampled. This has been fully considered but is not found to be persuasive. The gene amplification data presented in the specification were problematic. The control DNA was from blood rather than from a matched tissue sample (i.e., healthy lung), while the literature shows that matched tissue samples are the standard (Pennica et al., Konopka et al.). Also, the data were not corrected for aneuploidy, a phenomenon that occurs in cancerous and non-cancerous lung (Sen, Hittelman). Therefore, it is not clear that the reported amplification is significant. Furthermore, the lung tumor samples in which PRO290 was reported as being amplified were not of the same type. For example, PRO290 tested positive in LT11 and LT13 (p. 161). These are described in the specification as corresponding to stage IIA squamous cell carcinoma and stage IB adenosquamous cell carcinoma. Other lung tumor samples of the same types did not test positive for PRO290 gene amplification. Therefore, the relevancy of Applicants' comments regarding rare malignancies is not clear. If PRO290 were amplified in all stage IIA squamous cell carcinomas, for example, but no other lung carcinomas, such would appear to indicate that PRO290 was a significant rare malignancy marker for stage IIA squamous cell carcinoma. However, no such trend was disclosed. The specification does not disclose any special feature or prognosis, of lung or colon tumors that amplify the PRO290 gene compared to lung or colon tumors that do not amplify the PRO290 gene. It is left to the skilled artisan to determine the significance (if any) of such a difference. Such constitutes the type of further research required to bestow a substantial utility on the claimed invention.

On p. 7, Applicants refer to Orntoft et al., Hyman et al., and Pollack et al. as evidence supporting the assertion that gene amplification more likely than not correlates with increased polypeptide levels. Applicants characterize Orntoft et al. as studying transcript levels of 5600

genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicants characterize Hyman et al. as comparing DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. Applicants characterize Pollack et al. as profiling DNA copy number alteration across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that one average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold increase in mRNA levels. Applicants conclude that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Applicants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO290 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung cancer (see also previous Office action on page 6).

Applicants refer on pages 7-8 to the declaration of Dr. Polakis, previously submitted in this application under 37 C.F.R. § 1.132 and previously discussed by the Examiner on pages 7-8

of the last Office action mailed 11/9/04. Applicants characterize the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Applicants conclude that all of the submitted evidence supports Applicants' position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO290 (i.e., data regarding amplification of PRO290 genomic DNA), and does not disclose any information regarding PRO290 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), Haynes et al., Lian et al., and Fessler et al., all discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were

lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

Applicants argue that the sale of gene chips and their usefulness to the research community supports the utility of the instant invention. Applicants' arguments have been fully considered but are not found to be persuasive. First, the instant invention is not drawn to a gene chip but to a polypeptide. Second, chips do not in general have a specific and substantial utility because they are research tools like DNA libraries. Any individual nucleic acid in the chip or library has no more value than any other until significant further research is done to characterize it.

Applicants refer to the declaration of Dr. Ashkenazi on page 8 of the response, submitted under 37 C.F.R. § 1.132 and previously discussed in the last Office action mailed 11/9/04 on p. 8. In the declaration, Dr. Ashkenazi states that, even when amplification of a cancer marker gene does not result in significant overexpression of the corresponding gene product, the absence of gene product overexpression still provides significant information for cancer diagnosis and treatment. Applicants also refer to Hanna et al., previous cited, in which breast cancer diagnosis includes testing for HER-2/neu amplification and absence of HER-2/neu gene product overexpression. Applicants argue that such leads to a more accurate classification of the cancer and a more effective way of treating it. Applicants argue that the PRO290 polypeptide is also useful in tumor categorization (such as suggested by the Ashkenazi declaration and the Hanna et al. reference), the results of which become an important tool in the hands of a physician enabling the selection of treatment modality that holds the most promise for the successful treatment of a patient. This has been fully considered but is not found to be persuasive. While it may be true that lack of overexpression of a gene product can also provide useful information in tumor categorization, the specification does not disclose such further testing of PRO290 gene product expression levels. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products based on the claimed invention are not in "currently available" form. Furthermore, the specification provides no assertion that the claimed PRO290 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO290. This is also further experimentation that would have to be performed by

the skilled artisan, indicating that the asserted utility is not substantial. Finally, Hanna et al. supports the rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments to reasonably confirm the real world context of the asserted utility. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

Applicants argue (p. 8) that the teachings of Hanna et al. show that for Her-2, to diagnose breast cancer both gene product presence as well as amplification of the gene itself provides the most complete information. The argument has been fully considered, but is not persuasive. Hanna et al. say these tests are used more or less independently, with the protein test used first, followed by the gene test if the protein test is negative (col. 2, third full paragraph). The protein test is only necessary to determine the appropriateness of antibody therapy. Also, it is stated in the same paragraph that "In general, FISH [gene] and IHC[protein] results correlate well. However, subsets of tumors are found which show discordant results; i.e., protein overexpression without gene amplification or lack of protein overexpression with gene amplification. The clinical significance of such results is unclear." Therefore, the issues of Her-2 cannot be generalized to any gene expressed in a tumor.

Applicants argue (pages 9-10) that "the Hu et al. reference does not conclusively establish a *prima facie* case for lack of utility for the PRO290 molecule, for the reasons outlined....". Applicants also argue the data of Hu et al. provide little if any information about genes with less than 5-fold differential expression tumor compared to normal tissue. The argument has been fully considered, but is not persuasive. First, the Hu et al. reference was not relied upon alone, but in combination with other references that establish the unpredictability of correspondence in gene and encoded protein levels. While there are shortcomings of the technique used by Hu et al., the findings are suggestive of a correlation between expression level and activity. The caution provided in the last paragraph of p. 411 is noteworthy: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful."

Applicants conclude on pages 10-11 that, based on the gene amplification data presented for PRO290, there is ample support for the Applicants' position that increased gene amplification levels more likely than not predict increased mRNA and polypeptide levels. Applicants urge that one skilled in the art would reasonably expect, based on the gene amplification date, declarations, and supportive articles presented by Applicants that the PRO290 polypeptide is most likely to be concomitantly overexpressed in certain lung tumors and is therefore useful as a lung cancer marker. Applicants argue further that even if PRO290 polypeptide was *not* overexpressed in lung or colon tumors, PRO290 polypeptide would still be useful as a marker in tumor categorization and becomes a useful tool enabling the physician to decipher appropriate lines of treatment for the cancer patients. Applicants again argue that the art cited by the Examiner does not support the unpredictability and requirement for further significant research associated with the instant invention. This has been fully considered but is not found to be persuasive for four reasons. First, PRO290 genomic DNA was found to be amplified in only three out of fourteen lung cancer samples compared to a normal DNA control from blood. Gene amplification in lung tumors was not compared to a matched normal tissue sample, as is the standard in the art (see Pennica et al., Konopka et al.). The data were not corrected for aneuploidy, which was known to be common in cancerous and non-cancerous lung tissue (see Sen, Hittelman). Thus, it is not clear from the gene amplification data whether or not PRO290 genomic DNA actually is amplified in certain lung tumors. Second, the literature reports that gene amplification often does not correlate with increased mRNA levels (see Pennica et al., Konopka et al.). Third, the literature reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al., Lian et al., Fessler et al.) or cancerous tissue (see Hu et al., Hanna et al.). In view of the totality of the evidence, the skilled artisan would not reasonably presume that PRO290 polypeptide is overexpressed in certain lung or colong tumors based on the disclosure regarding gene amplification without actually testing for PRO290 polypeptide overexpression. The requirement for such testing indicates that the asserted utility is not substantial, *i.e.,* it is not in currently available form. Fourth, based on the gene amplification data, the skilled artisan *also* would not presume that PRO290 polypeptide is not overexpressed in certain lung tumors without actually testing for PRO290 polypeptide levels. In view of such and the lack of guidance regarding how the physician would use information

regarding PRO290 polypeptide overexpression, or lack of overexpression, in categorizing a tumor and choosing a treatment modality, the asserted utility for PRO290 polypeptide as a cancer diagnostic is not substantial. In view of the totality of the evidence, the rejections for lack of utility and enablement are proper.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (571) 272-0829.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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October 14, 2005

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